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Is thromboprophylaxis cost effective in ovarian hyperstimulation syndrome: a systematic review and cost analysis

Kelly Comerford Wormer, MD¹, Ayesha A. Jangda², Farah A. El Sayed, MPH³, Katherine I. Stewart, MD, MBA⁴, Sunni L. Mumford, PhD⁵, and James H. Segars, MD^{4,*}

¹UT Ob/GYN Center, 2010 Church Street, Nashville, TN, 37203

²Ziauddin University, Karachi, Pakistan

³Faculty of Medicine, American University of Beirut Medical Center, Riad El Solh, Beirut, Lebanon

⁴Department of Gynecology and Obstetrics, Johns Hopkins University School of Medicine, 600 North Wolfe Street, Baltimore, MD 21287, USA

⁵Epidemiology Branch, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, 6100 Executive Blvd, Bethesda, MD, 20892, USA

Abstract

Background—The majority of serious thromboembolic events occurring in assisted reproductive technologies (ART) are in women with ovarian hyperstimulation syndrome (OHSS).

Objectives—The purpose of this study was to present a thorough review and cost analysis regarding the use of VTE prophylaxis in OHSS to inform clinical management.

Data sources—Databases used were Pubmed and Embase, in addition to checking reference lists of retrieved articles (inception to November 2017).

Methods—The systematic search strategy identified 365 titles and abstracts. Articles included in the qualitative synthesis had identified venous thrombosis incidence rate ratios. A separate search for the cost model was conducted recognizing all associated complications of VTE. The decision tree was modeled to best fit the patient population and a sensitivity analysis was performed over a range of variables.

Results—The cost of VTE event per OHSS patient not on prophylaxis was €5,940 (range €3,405 to €8,727), versus €4,134 (€2,705 to €23,192) per event per patient on prophylaxis, amounting to

*Corresponding author: James H. Segars, MD. jsegars2@jhmi.edu Address: 720 Rutland Ave, Room 624 Ross, Department of Gyn/Ob, Johns Hopkins University School of Medicine, Baltimore, Maryland, 21205.

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Author's Roles

K.C.W. conducted research and prepared the original manuscript, F.S. and A.J. conducted research and assisted in revision and preparation of manuscript, K.S. conducted research and assisted in preparation of the manuscript. S.M. conducted research and statistical analysis, J.S. conceived the idea and study design, prepared the manuscript.

a saving of (€19 to €23,192) per VTE per patient. Sensitivity analysis found VTE prophylaxis to be cost effective if the incidence of VTE in the OHSS population was greater than 2.79%. Prophylactic therapy was cost effective through 16 weeks of treatment.

Limitations—OHSS is infrequent and hence, the incidence of VTE in patients with OHSS is low; therefore, the data used to inform the incidence of VTE in OHSS in the model carry some uncertainty. Further, low molecular weight heparin (LMWH) has side effects therefore individualization of care must be considered.

Conclusions—With the increasing incidence of infertility and requirement for ART, thromboembolism in OHSS poses a major health threat for patients. VTE prophylaxis using enoxaparin was cost effective in patients with severe OHSS over a wide range of costs and incidences. Prophylaxis was also cost effective through the completion of the first trimester of pregnancy.

Keywords

Ovarian hyperstimulation syndrome; venous thromboembolism; prophylaxis; cost analysis

Introduction

Ovarian hyperstimulation syndrome (OHSS) is a life-threatening complication of assisted reproductive technology (ART). Clinically significant moderate to severe OHSS occurs in 0.5 to 5% of all ovarian stimulation cycles [1]. A rare but devastating consequence of OHSS is thromboembolism, which can lead to permanent injury or death. Arterial and venous thromboemboli are associated with OHSS [2, 3]. Here, we focused on venous thromboembolism as it has been more thoroughly studied. The overall risk of VTE in pregnant women after in vitro fertilization (IVF) is reported to be 0.08 to 0.42% [4,5]. The risk of VTE is significantly higher in women with OHSS, ranging from 0.78 to 11% as cited in multiple studies [table 1].

The pathogenesis of OHSS has been intensely studied, but the exact mechanism remains unclear. Factors include serum estradiol [6, 7], vascular endothelial growth factor (VEGF) and the “third spacing” of fluid in OHSS [8, 9]. Increased intra-abdominal pressure [10], hemoconcentration with a decrease in circulating anticlotting factors [10], or estrogen-rich lymph collected from the ascites [11]. Hypercoagulable changes associated with pregnancy may also play a role [12,13]. Patients with OHSS and VTE are likely to be pregnant [14]. The administration of human chorionic gonadotrophin (HCG) for final oocyte maturation and triggering of ovulation may further augment the risk of VTE [15].

VTE is associated with significant morbidity and mortality. VTE can increase the cost and length of hospital stay, has high rates of recurrence, and can be fatal [16]. Post-thrombotic syndrome and chronic pulmonary hypertension, respective chronic complications of deep vein thrombosis (DVT) and pulmonary embolism (PE), lead to increased medical costs [17,18] and decreased quality of life [17]. In pregnancy, VTE may cause additional complications and increase the cost and requirements in the provision of antenatal care [19]. It is because of these risks that empiric thromboprophylaxis for OHSS is often used [19,20].

However, evidence supporting the cost effectiveness of thromboprophylaxis in ART or OHSS is lacking. In contrast, VTE prophylaxis was found to be cost effective for medical or surgical patients where the risk of VTE exceeded that associated with OHSS. The preventable cost of hospital acquired VTE was estimated to be €12 to €24.5 billion euros [18].

The purpose of this analysis is to present a thorough review and cost analysis regarding the use of VTE prophylaxis in OHSS to inform clinical management. We hypothesize that it is cost effective to provide VTE prophylaxis to OHSS patients.

Materials and Methods

VTE in patients with OHSS following ART

Literature search—A systematic search of the literature published in the PubMed and the Embase database, along with a hand searched reference list was conducted. The search encompassed all articles from the earliest indexing year until November 2017, in line with the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). The following MeSH terms were used: *ovarian hyperstimulation*, and *thrombosis* or *thromboembolism*, and *reproductive techniques*, assisted or *in vitro fertilization*. After acquiring initial search results, the titles and abstracts of the articles were evaluated for suitability. Full text articles were then retrieved and assessed for inclusion. Two authors (AJ, FS) independently accomplished the screening process and any disagreement was resolved by discussion between the investigators.

The patient, intervention, comparator outcome (PICO) question formulated for this study was as follows: In females with OHSS (P), does VTE prophylaxis (I) compared to no prophylaxis (C) affect the rate of VTE development (O)?

The primary objective was to systematically identify rates of VTE in OHSS to inform cost analysis and decision tree model.

Eligibility criteria—All case series, case-control, prospective and retrospective cohort studies were considered for inclusion when they reported rates of VTE development in either ART or OHSS. Only full text articles were included, poster presentations and oral communications were excluded. The search was limited to articles written in English with the exception of one pertinent Czech study which was included with the use of a translator. Articles reporting arterial thrombi, individual case reports, animal studies, and articles in which the incidence of VTE in OHSS or ART was not reported were excluded. Eligibility assessment of the retrieved articles was performed by two authors (AJ and FS) independently. In case of doubt or disagreement, a third author (KCW) was consulted to establish consensus. The flow diagram of the systematic literature search is shown in [Figure 1].

Data Extraction—Two independent authors (AJ and FS) extracted data independently on: author/s, year of publication, title of the article, study design, patient population including the number of patients with OHSS and incidence of VTE among them [Table 1]. Authors

were contacted in case additional information was needed. After the data was extracted, it was reassessed for discrepancy by the authors to minimize the possibility of error. Since the data on the topic is scarce, and the relevant articles were varied in study design, the quality of the obtained studies was not assessed.

Search Results—Primary search yielded 75 articles on PubMed, 321 articles on Embase and 4 articles from other sources (reference review). Thirty-one articles were identified as exact duplicates and were hence removed. After removal of the duplicates, 369 articles were screened for eligibility, of which 63 were selected for full-text assessment. From these records, 53 articles were excluded because they did not meet eligibility criteria (see above). In total, 10 articles were included for critical appraisal [Table 1].

Probability estimates and model assumptions

As OHSS is a rare phenomenon and VTE during OHSS is even more so, there are few studies reporting baseline incidence of VTE or the incidence after prophylaxis. Data on the incidence of VTE in patients with OHSS comes from case series and retrospective cohorts from which arterial thrombi were excluded as summarized in Table 1 [Table 1]. It should be noted that most reports do not include pharmacological data, and in those that do report prophylaxis [13,5] there was not a standardized prophylactic treatment regimen with regard to dosage or duration. In large cohort studies on the incidence of VTE in ART from 2012, [21,22] and from 2017 [23], data on medications and prophylaxis were not recorded. Due to uncertainty of dosing of hormonal treatment in the 1970s, we excluded the high rate of VTE found by Schenker and Polishuk [24].

Diagnosis of OHSS varied between the studies with some including only hospitalized patient [12,21,22], and some including only patients with severe OHSS [12,25]. One study by Dalvigne et al. classified OHSS as “disabling abdominal pain” without any other diagnostic criteria [13]. Only 8.9% of OHSS patients required paracentesis, so likely the number of severe OHSS patients was low and patients were only followed for several days after transfer [13]. Consequently, this study was excluded from our analysis.

We assumed a baseline risk of VTE in patients with OHSS of 4%, based on the study [5] and as cited by the American College of Chest Physicians (ACCP) [19]. This was used despite the fact that some patients received prophylaxis as it shows an average risk value in a relatively large population and has previously been used by a large accredited association as expert opinion [5,19]. In addition, a range of baseline risk (see Table 1, baseline VTE risk 2.5-10%) was included in the sensitivity analysis. As studies that have evaluated the efficacy of prophylactic therapy in this specific population are lacking, indirect evidence from a meta-analysis of thromboprophylaxis in women undergoing orthopedic surgery was used [26], as was similarly used by the ACCP in establishing its guidelines for prophylaxis in OHSS patient [19]. With this estimate, risk of VTE in women on prophylactic therapy would decrease to 1.4% [19]. This is in accordance with the findings of Rova et al. [21] reporting a 1.5-1.7% risk of VTE in OHSS patients if we assume the majority of patients were treated with thromboprophylaxis.

In a case series by Chan et al. [27] of women with OHSS who presented with VTE, 94% presented with DVT and 6% with PE. This was used in this study as the relative incidence of DVT to PE. Due to the high prevalence of upper extremity DVT and differing rates of complications with UEDVT, it was important to stratify patients based on these different rates [Table 2]. Different complications exist as well in patients with PE versus DVT, which Table 2 also outlines.

Risks of treatment with LMWH were based on current literature. The risk of a major bleed while on anticoagulant therapy was 0.2% [28], while the risk of fatality from a major bleed was 9% [29]. HIT is a rare complication of enoxaparin, occurring in 0.2% of the treated population [30,31]. Risk of mortality from HIT has been cited as 11% [32]. Risks were chosen to be in the VTE model on best fit for the population. Ranges of a selection of risks were identified in the literature and reflected in the sensitivity analysis [Supplemental Table 1]. The baseline risks of ART and other complications associated with OHSS were not included in this model.

Cost Estimates

The cost of medication for prophylaxis and treatment was determined with assistance from the National Institutes of Health clinical center pharmacy for wholesale pricing (Amerisource Bergen Drug corporation). Generic medication costs were used with the following assumptions: enoxaparin 40 mg at €23.80 per dose, and warfarin 5 mg at €0.09 per dose. Treatment costs utilized recommendations by general accord with large peer reviewed publications including ACCP guidelines [19,33], American Heart Association/American College of Cardiology [34] and American College of Obstetrics and Gynecology [35]. Cost of prophylaxis was determined by the cost of 6 weeks of once daily dosing of enoxaparin. Cost of treatment was determined by the cost of 10 days of twice daily dosing of enoxaparin, followed by six months of once daily dosing of warfarin. In pregnant patients, the cost of treatment was determined by the cost of twice daily dosing of enoxaparin for 46 weeks to include pregnancy and postpartum periods [19,33,34,35]. Pregnancy rates were factored directly into the cost of treatment. Although pregnancy rates for patients who develop OHSS are high, miscarriage rates are also significant. Studies cite clinical pregnancy rates of 59 to 73.2% with birth rates of 42 to 52% [12,36]. A conservative estimate of 42% pregnancy rate with OHSS was used and costs per event averaged accordingly.

Hospitalization costs and costs of complications were derived from the literature review. An additional search was performed using PubMed for the key words *cost* and *venous thromboembolism* or *thromboembolism*. Studies identified by the literature search were retrieved and reviewed and references were then reviewed for pertinent information.

All costs were converted to 2017 Euros based on the consumer price index (CPI). Average initial hospitalization cost of DVT was estimated to be €9,838 and of PE €14,195 [37]. Readmission and recurrence costs were estimated to be €1,902 for DVT and €14,822 for PE [37]. Post-thrombotic syndrome was reported to have a cost of €1,013 in the first year of treatment, followed by an annual estimated cost of €112 in subsequent years [38]. Chronic pulmonary hypertension was reported to have an annual cost of €2,805 [18,39]. A

conservative estimate of 30-year survival was assumed as the average age of women undergoing ART was 39 years old [40], and the average life expectancy of women was 77.8 years [41]. Morbidities typically present within 5 years of VTE [42,43], and the estimated lifetime cost of chronic pulmonary hypertension (CPHTN) was €381,441 and of PTS was €12,962. The cost of complications from enoxaparin were reported as €45,304 for HIT [30] and €6,040 [44]. Upper limits of costs included in the sensitivity analyses are shown in Supplemental Table 2.

Cost of premature death was determined from a human capital model that reflects present value of lifetime earnings, adding expected earnings in each year of life forgone based on the average life expectancy [45,46]. From this model, the cost of premature deaths in women 25-40 years old was averaged to accord with the average patient population of ART with OHSS for a cost of €2,369,511 [13,47,48].

Decision Tree model and Statistical Analysis

For the decision tree model, inputs were based on existing decision trees found in the relevant literature, and the structure was adapted from previous cost analyses of VTE including all relevant morbidities and mortality associated with VTE [18]. Our decision tree model incorporated factors relevant to OHSS population including differences in ratio of upper to lower extremity DVT. Changes were made due to the young, female patient population typical for OHSS, pregnancy rates, and differences in lower and upper extremity VTE and VTE-related complication rates. The decision tree contains probability information on: relative rates of DVT to PE, UEDVT to LEDVT, VTE recurrence and readmission, post thrombotic syndrome, chronic pulmonary hypertension, and risks of enoxaparin including heparin-induced thrombocytopenia (HIT) and bleeding. Calculations were performed using Microsoft Excel. Probabilities were based on information obtained from the literature review. The product of the event probability of each branch and cost of event were performed for each branch and the totals summed for cost of VTE with and without treatment.

The decision tree was modeled to best fit the patient population. Sensitivity analysis was performed over the range of several variables including rate of VTE, length of treatment, and cost of prophylaxis. One-way sensitivity analyses were first performed varying the incidence of VTE for OHSS patients both at baseline without prophylaxis and then with prophylaxis. Multivariable sensitivity analysis was performed to find the ranges of cost for the different outcomes. Both maximum and minimum rates and costs identified in the literature review were then used in the decision tree to find a range of VTE costs. The decreased relative risk of VTE expected in the prophylaxis population was maintained while the overall risk of VTE in the prophylaxis population was held constant at 1.4%.

Ethics Approval

We did not obtain Institutional Review Board approval since all data used in this analysis were based on published results or publicly accessible data.

Results

Cost effectiveness

The decision tree evaluated cost based on the assumed outcome of VTE. Based on the cost model [Figure 2], the cost of VTE including complications without prophylaxis was €5,935. Cost of VTE including complications with prophylaxis was €4,130. This resulted in an estimated cost savings of €1,804 per VTE event if prophylaxis was given based on the model assumptions, or a 1.4-fold reduction in cost with prophylaxis.

Sensitivity analysis

A one-way sensitivity analysis was performed varying the incidence of VTE for women not on prophylaxis from 1-11% while holding constant the incidence of VTE for women on prophylaxis at 1.4% [see Table 1]. The results are shown in Figure 3A. Prophylaxis was cost effective when the incidence of VTE for women not on prophylaxis greater than 2.79%. A similar sensitivity analysis was then performed varying the incidence of VTE for women on prophylaxis from 1-4% while holding constant the incidence of VTE for women not on prophylaxis at 4% [see Figure 3B]. Prophylaxis was cost effective when the incidence of VTE for women on prophylaxis was 2.62% or lower.

For the multivariable sensitivity analysis, rates and costs were adjusted to maximum values [see Supplemental Tables 1 and 2]. Rates of PE relative to DVT were maximized in all branches of the model, risk of VTE on prophylactic therapy was held constant (with a resulting change in relative risk reduction from 0.36 to 0.14), and all other rates and costs not listed were held constant. Cost of VTE with no prophylaxis was €38,698, and cost of VTE with prophylaxis was €14,722, a 2.6-fold reduction in cost with a projected savings of €23,637. A similar analysis was then performed holding the relative risk constant at 0.36, increasing the risk of VTE on prophylaxis to 3.6%. This resulted in a cost of VTE with prophylaxis of €23,175, a 1.7-fold reduction in cost with a projected savings of €15,523 per VTE event.

In a similar fashion, costs and rates were then adjusted to minimum values [see Supplemental Tables 1 and 2], with rates of PE relative to DVT minimized. Risk of death from HIT in this scenario was omitted as the percentage was negligible. Holding the percentage of VTE on prophylaxis constant, the cost of VTE with no prophylaxis was €3,402 and the cost of VTE with prophylaxis was €3,383 for a savings of 19 per VTE event. Holding the relative risk of prophylaxis constant, the cost of VTE on prophylaxis was €2,703, for a savings of €670 per VTE.

Time course of prophylaxis

There is a considerable variation in duration of prophylaxis, with reports varying between 6 and 12 weeks, depending on pregnant and non-pregnant states. To assess the duration of prophylaxis, the incidence of VTE for women on prophylaxis was varied over the time interval of 16 weeks to theoretical decreased incidences [Figure 3]. In Figure 3C, the incidence was reduced to 0.01% [RR 0.002-0.35] and in Figure 3D, the incidence of VTE for women on prophylaxis was reduced to 1% [RR 0.25-0.35]. In both of these models, cost

of VTE for a patient without prophylaxis was held constant, and the cost of enoxaparin prophylaxis increased linearly with each additional week of therapy. In Figure 3C, the average cost of VTE per patient on prophylaxis was much less than the average cost of VTE per patient not on prophylaxis for 16 weeks. In Figure 3D, the incidence of VTE for a patient on prophylaxis would have to be 1.49% or greater at 16 weeks to impact the cost effectiveness of prophylactic therapy. The model used 16 weeks as the maximum time course of prophylaxis to ensure cost effectiveness through greater than 12 weeks, which is the maximum time course reported in the literature.

Discussion

The design and utilization of the decision tree cost-effectiveness model in our study revealed that thromboprophylaxis in patients with severe OHSS was cost effective over a wide range of plausible, data-driven scenarios. Up to nearly two-fold reduction in cost was seen across multiple incidence rates and costs scenarios. It is clear based on the patient population of predominantly young, healthy women that the cost of permanent injury or death due to VTE was significant.

Strengths of this VTE cost model lie in the inclusion of a wide range of costs and incidences of VTE obtained from current literature. Next, the model gives a reflection of a specific patient population, taking into account the increased cost of treatment during pregnancy and the increased incidence of upper extremity DVT in patients with OHSS. Conservative estimates were used in the base model for an accurate prediction of societal costs of VTE. The multivariable sensitivity analysis was performed to give a range of costs and incidences. Previous cost analyses in the literature on thromboprophylaxis by experienced clinicians provided a framework upon which assumptions were based [18].

Length of treatment was also an important issue addressed in this cost analysis. In previous reviews in the literature, VTE in patients with OHSS was found to occur 40-46 days after embryo transfer [3,14,23]. In OHSS patients that are pregnant there was a tenfold increased risk of first trimester VTE [22], consistent with previous reports [14]. Four to eight weeks of prophylactic therapy for the non-pregnant OHSS patient has been suggested [49] consistent with ACCP guidelines [19]. Thus, we assumed a duration of 16 weeks into the pregnancy as the time period for prophylaxis when the theoretical risk of VTE would be most effectively minimized. Our cost analysis showed that prophylaxis through the first trimester of a pregnancy was cost effective.

Enoxaparin was used in this cost analysis as recommended for pregnant patients by ACCP guidelines, however unfractionated heparin (UFH) is a safe and effective alternative [19]. The cost of six weeks of treatment with UFH is approximately 6 times less than treatment with enoxaparin, which would favor prophylaxis even more strongly.

The primary weakness of any decision tree analysis is the design, which is limited by assumptions and fixed outcomes. Here, we sought to minimize this by an extensive review of literature, which obtained ranges of rates of events and costs from multiple sources. Only major episodes of bleeding were included; episodes of minor bleeding were excluded from

the decision tree due to the minimal cost differences they would give between the groups and the low bleeding risk post ART procedure [50]. It is reasonable to consider thromboprophylaxis in less severe cases of OHSS, and our sensitivity analyses demonstrate a cost effectiveness over a range of baseline risks.

Some studies have suggested that in the OHSS population thromboprophylaxis may not be as effective, with extension of clots occurring despite prophylaxis in up to 10% of reported cases [14]. In a very recent systematic review conducted by Sennstrom et al., it was concluded that the risk of VTE after IVF is doubled. Just as our study suggests, it was recommended that IVF patients with OHSS be prescribed LMWH during the first trimester [71]. Hence this topic should be investigated further in future studies.

In conclusion, our findings support that thromboprophylaxis is cost effective and should be considered for all patients with severe OHSS. Prophylaxis was cost effective over a prolonged course and even through the first trimester of pregnancy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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*Exception: 1 Czech study included by use of translator

Figure 1.

Flowchart of identification and selection of studies for the systematic review. PRISMA flow diagram of the systematic literature search. n = number.

Figure 2.

Cost model decision tree. The left side (white boxes) illustrates the events and subsequent risks of VTE with enoxaparin prophylaxis in OHSS patients. The right side (grey boxes) illustrates the events and risks with no thromboprophylaxis. Abbreviations: CPHTN, chronic pulmonary hypertension; DVT, deep vein thrombosis; HIT, heparin induced thrombocytopenia; LEDVT, lower extremity deep vein thrombosis; LMWH, low molecular weight heparin; NC, no complications; PE, pulmonary embolism; PTS, post-thrombotic syndrome; R/R, recurrence/readmission; UEDVT, upper extremity DVT; VTE, venous thromboembolism

Figure 3.

Sensitivity analysis. The dashed line in all four graphs represented average cost of VTE not on prophylaxis. The solid line represented average cost of VTE on prophylaxis. Figure 3A varied the incidence of VTE for OHSS patients not on prophylaxis (1-11%) with a set incidence of VTE for women on prophylaxis (1.4%). Prophylaxis was cost effective when the incidence of VTE for women not on prophylaxis was greater than 2.79%. Figure 3B varied the incidence of VTE on prophylaxis (1-4%) while keeping the incidence of VTE for patients not on prophylaxis constant (4%). Prophylaxis was cost effective when the incidence of VTE for women on prophylaxis was 2.62% or higher. Figures 3C and 3D varied the length of prophylactic therapy up to 16 weeks. Figure 3C varied the incidence of VTE for women on prophylaxis to 0.01%, and Figure 3D varied the incidence of VTE for women on prophylaxis to 1%. Both figures 3C and 3D showed prophylaxis to be cost effective to 16 weeks and beyond.

Abbreviations: VTE, venous thromboembolism; PPX, prophylaxis

Table 1

Incidence of VTE in OHSS populations

Study	Year	Study Design	Patient Population, OHSS (n), VTE (n)	Ratio of VTE/OHSS	% VTE in OHSS
Schenker and Polishuk, 1975	1968–1973	Case Series	18 patients, all with OHSS, 2/18 with VTE	2/18	11.1
Delvigne <i>et al.</i> , 1993	1988–1991	Case Control	128 patients with OHSS, 256 controls, 1/128 with VTE	1/128	0.78 ^a
Abrahamov <i>et al.</i> , 1998	1987–1996	Retrospective Cohort	163 patients, all with severe OHSS, 4/163 with VTE	4/163	2.5 ^b
Serour <i>et al.</i> , 1998	1998	Retrospective Cohort	3500 treatment cycles, 206 patients with moderate OHSS (5.9%), 60 patients with severe OHSS (1.7%), 4 patients with VTE, all had severe OHSS	4/60	Severe OHSS: 6 ^b All OHSS: 1.5
Dulitzky <i>et al.</i> , 2002	2002	Case Control	20 patients with severe OHSS, 41 controls, 2/20 with PE	2/20	10 ^b
Mara <i>et al.</i> , 2004	2004	Retrospective Cohort	2748 treatment cycles, 49 patients with OHSS (1.8), 3 patients with VTE, 2 in women with OHSS (2/49)	2/49	4.1 ^{ab}
Hansen <i>et al.</i> , 2014	1994–2005	Retrospective Cohort	31,098 patients 75,598 cycles, 715 patients with OHSS (1%), no patients had VTE	0/715	0
Rova <i>et al.</i> , 2012	1998–2008	Retrospective Cohort	964,532 deliveries, 1114 fresh IVF + OHSS; 1272 all IVF + OHSS. 19 VTE occurred, all in patients with fresh IVF cycles.	19/114	Fresh IVF: 1.7 All IVF: 1.5
Hansen <i>et al.</i> , 2014	1995–2005	Retrospective Cohort	16191 patients, 18787 pregnancies, 549 patients with OHSS, 36 patients with VTE, 5 in women with OHSS (5/549)	5/549	0.91
Villani <i>et al.</i> , 2017	2002–2011	Retrospective Cohort	661 patients, 1836 cycles, 49 patients with OHSS, 5 patients with VTE, 2 in women with OHSS (2/49)	2/49	4.1 ^a

Abbreviations: n: number, IVF: in vitro fertilization; OHSS: ovarian hyperstimulation syndrome; VTE: venous thromboembolism

^aProphylaxis reported (no data on duration or dosage)

^bUsed in sensitivity analysis

Table 2

Incidence of VTE and VTE-related events

Event	Probability with UEDVT	Probability with LEDVT	Probability with PE
Recurrence/Readmission	0.14 (Flinterman <i>et al.</i> , 2008)	0.05 (Spyropolous and Lin, 2007)	0.053 (Spyropoulos and Lin, 2007)
Post-thrombotic syndrome	0.15 (Elman and Kahn, 2006; Prandoni <i>et al.</i> , 1997)	0.17 (Prandoni <i>et al.</i> , 1996; Ashrani and Heit, 2009)	n/a
Chronic pulmonary hypertension	n/a	n/a	0.04 (Pengo <i>et al.</i> , 2004; Dentali <i>et al.</i> 2009)
Death	0.07 (Flinterman <i>et al.</i> , 2008)	0.09 (Douketis <i>et al.</i> , 1998; Carrier <i>et al.</i> , 2010)	0.082 (Park <i>et al.</i> , 2009)

Abbreviations: LEDVT, lower extremity deep vein thrombosis; DVT, deep vein thrombosis; PE, pulmonary embolism; UEDVT, upper extremity deep vein thrombosis

^aProbability after exclusion of patients with malignancy